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(54) Transdermal composition containing selegiline.

(57) The invention concerns an anhydrous transdermal preparation comprising in a 20-100% lyotropic liquid crystalline arrangement:

5-15 w.% of optically active or racemic N-methyl-N-(phenyl-2-propyl)-2-propynylamine or N-methyl-N-(1-(4-fluoro-phenyl)-2-propyl)-2-propynylamine or their therapeutically acceptable salts,

40-70 w.% of liquid polyoxyethyleneglycol,

10-20 w.% of solid polyoxyethyleneglycol,

2-30 w.% of a nonionic surface active agent,

2-20 w.% of propyleneglycol,

if desired 0.5-2 w.% of a polymer the a value of which is > 0.6, and if desired other auxiliary agents.

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The invention relates to an anhydrous transdermal composition, containing the active ingredient and the auxiliary materials in a 20-100 % lyotropic liquid crystalline arrangement.

In the case of certain therapeutical active ingredients it is well known that the application in a transdermal form has its advantages. Depending on the release constant of the active ingredient from the transdermal composition the required amount of active ingredient to treat the given disease and the active ingredient release assuring constant blood level can be ensured for a period of 1 day to 1 week.

It is known from the literature, that the monoamine oxidase-B and dopamine reuptake inhibiting compound Deprenyl can be successfully applied to slow down the development of Parkinson's disease on human in early stage,/Tetrud JW, Langston JV.: The effect of Deprenyl (Selegi-line); The natural history of Parkinson's disease, Science 1989., 245 514-522.; The Parkinson Disease Study Group: Effect of Deprenyl on the progression of disability in early Parkinson disease, N. Engl. J. Med. 1989. 321 1364-71/,administered in combination with L-Dopa containing preparations in the late phase of Parkinson's disease (Birkmayer:Deprenyl (Selegiline) in the treatment of Parkinson's disease. Acta Neurologica Scand. 1983 Supp. 95 103-106), in certain cases of schizophrenia (published PCT application No. 90/01298/ and according to the latest test results in dementia of Alzheimer type (Pierre N.Tariot, MD., Robert M.Coken MD. PhO, Trey Sunderland M.D.: 1-Deprenyl in Alzheimer's disease. Arch. Gent. Psychiatry Vol. 44. May 1987; P.N. Tariot, T. Sunderland: Cognitive effects of 1-Deprenyl in Alzheimer's disease: Psychopharmacology (1987) 91: 489-495; Gian Luigi Piccini, Giancarlo Finali, Massimo Piccirilli: Neuropsychological Effects of 1-Deprenyl in Alzheimer's type Dementia. Clinical Neuropharmacology Vol. 13, No. 2. pp. 147-163; E. Martiny, I. Pataky, K. Szilágyi, V. Ventor: Brief Information on an early phase II. Study with Deprenyl in demented patients Pharmacopsychiatr. 20 (1987) 256-257./

U.S. patent specifications No. 4,868,218 and 4,861,800 and PCT patent specification WO No. 89/09051 describe the possibility of transdermal application of Deprenyl. According to the disclosure of the patent specifications, any known, usually applied liquid or solid transdermal basic system is suitable for the transdermal administration of Deprenyl.

Studying the compositions published in the above mentioned literatures,other traditionally applied o/w emulsifying ointment bases, w/o emulsifying ointment bases and hydrogels respectively, we have found that the active ingredient was not absorbed at all, or it was already absorbed completely within some hours.

We set it as an aim to prepare a dermal preparation which assures a sufficient and uniform release of the active ingredient for at least 24, advantageously for 72 hours to treat the disease.

It is known further, that some surface active agents applied in transdermal basic ointments, e.g. decaethyloxide-oleylether (Brigj 96) form liquid crystalline system with water. In these creams the polyethyleneoxide chain of the surface active agent and the water form a continous hydrophilic area, which plays a well - defined role in the diffusion of the active ingredient.

By varying the water surface active agent ratio the liquid crystalline system and thereby the active ingredient diffusion can be influenced. (Journal of Controlled Release, 13 (1990) 73-81).

Surprisingly we have found, that in the case of a suitable composition even in an anhydrous medium a lyotropic liquid crystalline system can be formed. By varying the quantity of some components the particle size of the liquid crystals, and the ratio of the liquid crystalline arrangement compared to the total system can be influenced. In that way transdermal systems, ensuring uniform active ingredient release for 24, 48 and 72 hours, corresponding to the therapeutic demand, can be prepared.

According to the aboves, the present invention relates to an anhydrous transdermal composition containing in a 20-100 % lyotropic liquid crystalline arrangement:

1-30 w. % of optically active or racemic N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine (furtheron Deprenyl), or N-methyl-N-(1-(4-fluoro-phenyl)-2-propyl)-2-propyl-amine or the therapeutically suitable salts of them,

40-70 w. % of liquid polyoxiethylene,

10-20 w. % of solid polyoxiethylene,

2-30 w. % of a nonionic surface active agent,

2-20 w. % of propyleneglycol, if desired

0.5- 2 w. % of a polymer the a value of which is > 0.6, and if desired other auxiliary agents needed to 100 w. %, as emulsifying agents.

As liquid polyoxiethylene in the composition polyoxiethylen 200-600, preferably polyoxiethylen 400 and as solid polyoxiethylene, polyoxiethylene 1500-6000, preferably polyoxiethylene 4000 can be applied. For non ionic surface active agent e.g. polyoxiethylene-fatty-acid-ethers, polyoxiethylene-fatty-acid-alcohols, polyoxiethylene-fatty-acid-esters, sorbitan-fatty-acid-esters, polyoxiethylene-castor-oils, preferably polyoxiethylene-fatty-acid-ethers can be applied.

As another auxiliary material, as for example as emulsifying agent, polysaccharide can be used.

As a polymer such an agent can be applied coilness characterizing a value of which is > 0.6, for example polyoxiethylene 35.000.

The coilness i.e. permeability of the polymer, can be characterized by the a exponent of the Kuhn, Mark, Honwick equation describing relation between frontviscosity and molecular mass (see: Rohrsetzer S., Kolloidika, Tankönyvkiadó 1986, D.J. Shaw: Introduction to colloid and surface chemistry, Műszaki Könyvkiadó 1986, in Hung.).

The composition according to the invention can be prepared as follows: Warming up the liquid polyoxiethyle, adding the solid polyoxiethylene in melted form, then adding the surface active material and active ingredient warm dissolved in polyethylene glycol, cooling the mixture and adding the polymer and if desired the other auxiliary agents.

The active ingredient applied in the composition can be prepared according to the European specifications No. 0186680 and 0099302.

The abovementioned transdermal composition is applied in the treatment on the skin surface in the required dose, thereafter the treated surface is covered e.g. with plaster.

Because of the low dose-demand (5-10 mg/day) of the active ingredient we could not determine the blood-level directly, therefore we determined partly indirectly by a biochemical method the monoamine-oxidase (MAO) inhibiting effect of the active ingredient in the brain and liver tissues, and partly the quantity of the unabsorbed active ingredient from the plaster by HPLC.

The aim of these studies was to determine absorption parameters of the transdermal preparations of different composition. As a model rats and beagle dogs depilated on the required surface were used. Absorption kinetic was followed by determining the quantity of the unabsorbed active ingredient (HPLC). Besides we measured the monoamine oxidase (MAO) inhibiting effect of the absorbed active ingredient in rat brain and liver tissues.

Test methods: MAO activity of rat brain and liver tissues was determined by the radiometric method of Wurtman and Axelrod (Biochem. Pharmacol. 1963. 12, 1417). The remaining active ingredient content of the plasters removed from the test animals - was determined by HPLC, the numerical results were obtained by calibration prepared from different quantities of an ointment.

Results and evaluation of the data: In rat studies the extent of monoamine oxidas-B enzyme inhibition shows that the active ingredient missing from the plaster determined by HPLC was absorbed. Table I contains the results of these measurements.

The absorption velocity measured on rat skin shows that the skin of rats is not suitable as a kinetic mode, since most of the preparations are absorbed within 1 hour. A more suitable model is the beagle dog. In this case by measuring the remaining active ingredient by HPLC we have found quickly, respectively slowly absorbable active ingredient containing ointments. The results are shown in Table II.

Table I

Effect of Deprenyl (1 mg/kg s.c.) and UG85 Deprenyl-plaster (3 mg/kg) on the inhibiti n of MAO-B activity (%) as compared to the control. Measurements were mad in rat brain- and liver nucleus free homogenates with ^{14} dC-PEA substrate. ± S.D. (n = 9[x])				
brain		plaster	liver	
time	s.c.		s.c.	plaster
0'	0	0	0	0
5'	-	9.6± 6.86	-	0
15'	-	45.07±13.72	-	14.23±20.80
30'	-	60.60± 3.84	-	12.80±15.25
45'	-	66.91± 1.88	-	45.10±10.48
1 hour	79.02± 1.58	73.09± 5.05	63.23±11.98	58.93±19.08
2 hours	87.09± 2.05	53.22± 3.42	74.94± 1.10	69.63± 6.94
4 hours	86.74± 3.00	55.30± 2.96	57.63± 5.23	52.80± 9.29
6 hours	83.04± 1.46	41.49± 3.50	67.86± 9.22	57.06± 4.68
24 hours	89.36± 2.60	80.50± 3.24	86.04± 7.81	80.19± 3.74
48 hours	73.59± 1.77	72.05± 2.54	64.34± 8.11	86.65± 2.26
72 hours	76.99± 3.38	76.56± 1.13	68.54± 5.25	79.09± 2.59
96 hours	69.19± 3.58	56.00± 2.37	54.75±11.58	65.59± 7.04
7 days	32.20± 5.45	32.15±12.49	56.44± 7.59	55.33±11.69
9 days	13.56 + 1.97	18.16± 5.22	44.26± 3.45	47.66± 5.43
11 days	0.63± 0.95	14.88± 2.92	26.27±15.77	39.18± 4.34
14 days	0	0	24.22± 3.13	0

[x]: 3 animals and 3 parallel measurements at a given time

Table II

Transdermal absorption of Deprenyl in beagle dogs		
Ointment	Duration of experiment (hours)	Remaining Deprenyl %±S.D.
Ug 85	24	9.6± 1.5
Ug 110	24	34.9±15.3
Ug 111	24	1.7± 2.2
Ug 118	24	13.4± 6.6
Ug 167[x]	4	75.7± 6.8
Ug 167[x]	24	40.6± 4.9
Ug 325	24	58.5± 4.1
Ug 325	48	28.3±12.1
Ug 325	72	8.4± 2.4

In further experiment we determined in domestic pigs the MAO activity in the brain and the platelet MAO-B activity.

The experiments were carried out on female (big white) domestic pigs, weighing 25-30 kg. The pigs were caged separately during the experiments, and the same food was supplied, which was used formerly.

Animals in the first group were treated orally with 10 mg of (-)-deprenyl in a gelatinous capsule. Blood samples were taken for the determination of MAO-B activity at: 0, 3, 6, 24, 48, 72 and 96 h. At 96 h after blood sampling the pigs were killed and the MAO-B and MAO-A activity was determined in their dissected brain.

The second group was treated with the UG-111 transdermal pr paration containing 10 mg (-)-deprenyl. The tim s of blood sampling w re at: 0, 3, 6, 24 and 48 h. Th transdermal pr parations wer removed at 24 h. For th det rminations of the residual (-)-deprenyl content of the pr parations the patch and its neylon cover wer used. Th skin was washed with ethanolic cotton - wool, which was also used for HPLC

determination. The pigs were killed at 48 h and MAO-A and MAO-B activity of the brain was determined.

The third group of the pigs was treated with UG-167 containing 20 mg of (-)-deprenyl. Blood samples were taken at: 0, 3, 6, 24, 48 and 72 h. The patches were removed at 48 h and the whole procedure described at group 2 was accomplished.

The blood was taken from the v. cava cranialis with a 20 ml plastic syring containing 1.5 ml 7.6 % Na-citrate solution. The volume of the blood taken was 18.5 ml at very time of sampling.

MAO activity was measured radiometrically according to the methods of Wurtman and Axelrod (Biochem. Pharmacol. 12. 1414-19; 1963) with a slight modification (K. Magyar in: Monoamine Oxidases and their Selective Inhibition. Ed.: K. Magyar, Pergamon Press, Akadémiai Kiadó, Budapest 11-21; 1980).

The method described by Willberg and Oreland was followed for platelet preparation (Med. Biol., 54: 137-44; 1976).

The results of the inhibition of MAO-B activity of the platelet after p. os and transdermal application are shown in Table III.

Table III. Effect of (-)-Deprenyl on the inhibition of MAO-B activity of the platelets (%) as compared to the control. Measurements were made with ^{14}dC-PEA substrate. ± S.D. (n = 3)

mode of application		time 3	6	24	48	72
		97.77	86.04	100.00	82.67	72.32
		92.52	96.51	100.00	70.48	65.63
per os	1	0.0	95.63	100.00	69.93	50.17
(10 mg)		95.15	92.73±3.35	100±0.0	74.36±4.16	52.71±6.56
UG-111		0.0	36.27	52.68	60.70	-
trans-	2	54.80	86.47	86.02	92.03	-
dermal		95.66	95.47	93.76	98.63	-
(10 mg;24h)		75.23	72.74±18.42	77.49±12.6	83.79±11.7	
UG-167		23.29	55.77	90.94	88.56	100.00
trans-	3	72.11	95.90	98.54	91.44	89.34
dermal		65.81	65.05	0.0	90.57	75.02
(20 mg;48h)		53.74±15.33	72.24±12.13	94.74	90.19±0.85	88.12±7.24

The results of the determination of MAO activity in the brain are shown in Table IV.

Table IV. Effect of (-)-Deprenyl on the inhibition of MAO-activity (%) as compared to the control. Measurements were made in dom stic pig brain nucl ous free homogenates with ^{14}C-PEA; ^{14}C-5-HT substrate. ± S.D. (n = 3)

mode of application	brain	
	^{14}C-PEA	^{14}C-5-HT
p. os (96 h)	73.22± 8.13	20.14± 6.0
UG-111 (48 h) transdermal(24 h)	56.31±10.03	16.39± 8.77
UG-167 (72 h) transdermal(48 h)	86.76± 6.67	18.50± 3.81

In table V. the transdermal absorption is shown.

Table V

Transdermal absorption of Deprenyl in domestic pigs as compared to the control.		
preparation	Duration of experiments (hours)	Remaining Deprenyl % ± S.D.
UG-111	24	14.2± 5.5
UG-167	24	36.5± 9.3
UG-167	48	6.1± 5.1

The composition, particle size, the percentage of liquid crystalline state of the different preparations was as follows:

UG-85	
Polyoxiethylene-glycol(PEG) 4000	60.0 g
PEG 200	100.0 g
Propyleneglycol	30.0 g
Deprenyl	3.0 g
PEG 400 ad	300.0 g
Average particle size: 9 micron; liquid crystalline state: 28 %.	

UG-111	
PEG 4000	16.0 g
PEG 400	60.0 g
Propyleneglycol	8.0 g
Cremophor EL	2.0 g
Deprenyl	5.0 g
PEG 400 ad	100.0 g
Average particle size: 72.7 microns; liquid crystalline state: 20 %.	

UG-118	
PEG 4000	16.0 g
PEG 400	60.0 g
Propyleneglycol	8.0 g
Cremophor EL	2.0 g
Deprenyl	5.0 g
Myritol 318	3.0 g
PEG 400 ad	100.0 g
Average particle size: 36.4 microns; liquid crystalline state: 50 %.	

UG-110	
PEG 4000	15.0 g
PEG 400	60.0 g
Propyleneglycol	10.0 g
Deprenyl	5.0 g
Cremophor EL	5.0 g
PEG 400	5.0 g

UG-167	
PEG 4000	19.0 g
PEG 400	55.0 g
Propyleneglycol	8.0 g
Xanthan gum	10.0 g
Deprenyl	5.0 g
PEG 400 ad	100.0 g
Average particle size: 91-109 microns; liquid crystalline state: 70-80 %	

UG-325	
PEG 35.000	1.0 g
PEG 4000	15.0 g
PEG 400	53.5 g
Propyleneglycol	4.5 g
Xanthan gum	15.0 g
Deprenyl	5.0 g
Cremophor EL	6.0 g
Liquid crystalline state: 100 %.	

Composition of the auxiliary-agents:
Cremophor EL: glycerin-polyethyleneglycol-ricinoleate
Myritol 318: trigliceride
Xanthan gum: polysaccharide

Claims

1. An anhydrous transdermal composition comprising in a 20-100% lyotropic liquid crystalline arrangement:

   5-15 w.% of optically active or racemic N-methyl-N-(phenyl-2-propyl)-2-propynylamine or N-methyl-N-(1-(4-fluoro-phenyl)-2-propyl)-2-propynylamine or their therapeutically acceptable salts,
   40-70 w.% of liquid polyoxyethyleneglycol,
   10-20 w.% of solid polyoxyethyleneglycol,
   2-30 w.% of a nonionic surface active agent,
   2-20 w.% of propyleneglycol,
   if desired 0.5-2 w.% of a polymer the $\underline{a}$ value of which is > 0.6, and if desired other auxiliary agent(s) as emulsifying agent(s).

2. A process for the preparation of a composition according to claim 1 which comprises adding the active ingredient(s) to a mixture containing the liquid polyoxyethyleneglycol, the solid polyoxyethyleneglycol, the nonionic surface active agent and the propyleneglycol to prepare a lyotropic composition having a liquid crystalline arrangement, to which if desired the said polymer and other auxiliary agent(s) are added.

3. A method of increasing the efficacy of a transdermal composition containing 5-15 w.% of optically active or racemic N-methyl-N-(1-phenyl-2-propyl)-2-propynylamine or N-methyl-N-(1-(4-fluorophenyl)-2-propyl)-2-propynylamine or their therapeutically acceptable salts characterised in that the active ingredient is applied to the surface of the skin in the form of a 20-100% lyotropic liquid crystalline composition.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 3341

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	WO-A-8 909 051 (SANDOZ) * Claims; page 7, example *	1-3	A 61 K 31/135 A 61 K 9/127 A 61 K 47/10
D,A	EP-A-0 406 488 (SOMERSET) * Claims; page 3, example 1 *	1-3	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	15-06-1992	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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